Molecular Therapy
Oncology
Commentary

Innovative approaches to glioma treatment: Oncolytic foamy virus and CAR T cell therapy

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https://doi.org/10.1016/j.omton.2024.200876

Cancer immunotherapy has garnered considerable attention due to the development of novel therapeutic strategies. Although the oncolytic potential of viruses has been recognized for a long time, recent years have seen a surge in interest surrounding oncolytic virotherapy. This renewed focus is driven by advancements in our understanding of viral biology and tumor immunology, which have paved the way for innovative research in the field. A defining characteristic of oncolytic virotherapy is its selective targeting of tumor cells, distinguishing it from other systemic therapies.[1] The combination of oncolytic viruses (OVs) with existing approved treatments represents a promising approach for tackling aggressive cancers.

In this context, the study by Tonne and colleagues, featured in the current issue of *Molecular Therapy Oncolytics*, presents a novel strategy to enhance the efficacy of immunotherapy against solid tumors, with a particular focus on high-grade gliomas (HGGs). These tumors have proven resistant to conventional treatments, making them a significant challenge in oncology. The authors explore the synergy between chimeric antigen receptor T cells (CAR T cells) and an oncolytic foamy virus (oFV) engineered to display the model CAR target antigen CD19 on tumor cells.[2]

HGGs are the most prevalent malignant brain tumors and are associated with a dismal prognosis despite advancements in therapeutic modalities. The current standard of care involves maximal surgical resection, followed by 6 weeks of radiotherapy in conjunction with temozolomide (TMZ) chemotherapy, and subsequent adjuvant TMZ therapy. However, several challenges, including tumor recurrence, the blood-brain barrier, and the complex tumor biology, limit treatment success. Furthermore, the immunosuppressive nature of the tumor microenvironment presents additional hurdles, underscoring the urgent need for therapies that can overcome these immunosuppressive mechanisms.[3]

In this study, Tonne and colleagues developed two oFV vectors, oFV-Δbel2 and oFV-bel2, to evaluate the efficiency of viral CD19 spread and therapeutic efficacy in a subcutaneous mouse model of HGG. This research is particularly significant, as it explores the use of oFV as a therapeutic platform for HGG, capitalizing on its broad tissue tropism and ability to infect quiescent cells. These characteristics make oFV a promising candidate for targeting residual disease following aggressive chemotherapy.

The study aimed to enhance the efficacy of oncolytic virotherapy by combining it with CAR T cell therapy. The approach involved engineering the oFV-Δbel2 and oFV-bel2 vectors to express a model CAR target antigen, hCD19t, in glioma cells. This strategy was intended to ensure that virus-infected cancer cells, which were not initially killed, could express the CAR target antigen and subsequently be neutralized by CAR T cells, thereby eliminating cancer cells resistant to oncolysis (Figure 1). The findings revealed that while CAR T cells effectively reduced oFV-specific bioluminescence, indicating the clearance of virus-infected tumor cells, the highest therapeutic efficacy was observed with high doses of oFV alone, in the absence of CAR T cells. This suggests that CAR T cell-mediated clearance of oFV might inadvertently reduce the desired oncolytic effect by limiting the virus's ability to spread within the tumor.

Despite this challenge, the study opens important avenues for future research. OVs hold significant potential to overcome tumor-induced immunosuppression, enabling infected tumor cells to express target antigens that can be effectively recognized by CAR T cells. Specifically, combining oFV-hCD19t with anti-CD19 CAR T cells could be integrated with other therapeutic modalities, such as chemotherapy or alternative viral platforms. Given that chemotherapy is often the standard of care in clinical settings, it could be followed by oFV-hCD19t and anti-CD19 CAR T cell therapy to specifically target residual disease. Moreover, the unique ability of the foamy virus to target quiescent cells, which are less likely to be eliminated by chemotherapy, presents a promising strategy for treating aggressive cancers like HGGs.[4] However, combining multiple therapies necessitates identifying the appropriate timing to achieve a synergistic effect, ensuring that one therapy does not hinder the efficacy of the other. In this study, the OV was administered first, followed by CAR T cell therapy after an 11-day interval. Given the slow replication rate of oFV-hCD19t, it would be interesting to explore whether a longer period between the two therapies could have allowed the virus to replicate more effectively, reduce tumor burden, stimulate the immune environment, and create a more favorable setting for CAR T cell therapy to succeed. The timing of OV and CAR T cell administration is a crucial factor that can significantly impact treatment outcomes.[5] Notably, an experimental study demonstrated that OV-associated type I interferon (IFN) negatively affects CAR T cell viability and that making CAR T cells insensitive to type I IFN enhances combination therapy.[6] The optimal timing between viral infection and adoptive cell therapy depends on factors such as virus replication rate and clearance, warranting further

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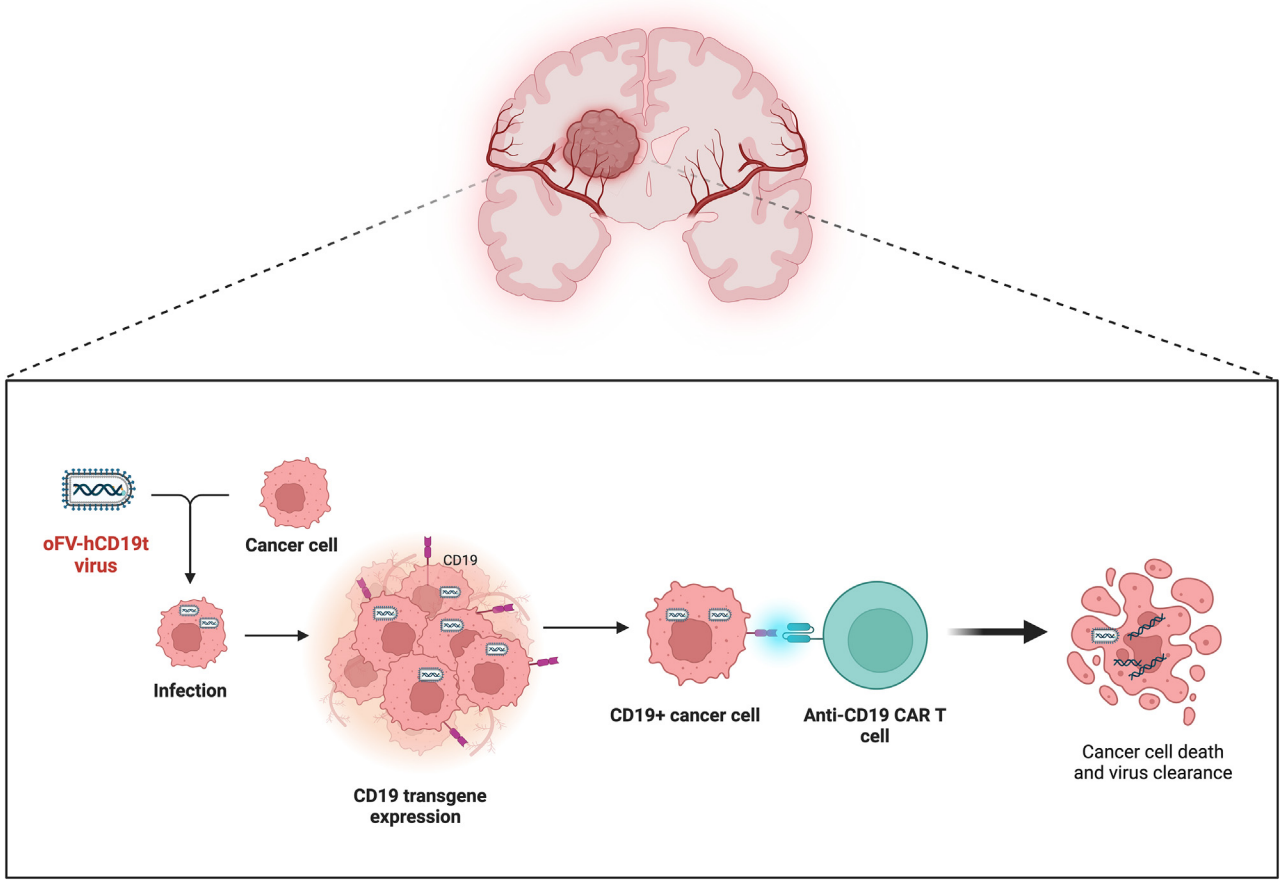

Figure 1. Mechanism of action of the oFV-hCD19t with anti-CD19 CAR T cells

Upon intratumoral injection, oFV-hCD19t is expected to selectively replicate within cancer cells, leading to their destruction, while concurrently expressing the CD19 CAR target antigen on the surface of these cells. Anti-CD19 CAR T cells can then recognize and eliminate CD19-positive tumor cells as well as cells infected with the virus.

investigation to determine the best combination with CAR T cells.

Several phase 1 and 2 clinical trials are currently investigating the effects of OVs in the treatment of HGGs. Notably, a phase 1 clinical trial (ClinicalTrials.gov: NCT02444546) is exploring the combination of Reolysin, a reovirus administered intravenously, with subcutaneous sargramostim (granulocyte-macrophage colony-stimulating factor [GM-CSF]) in patients with HGG. Additionally, other OVs, such as herpes simplex virus 1 (HSV-1), are being tested with alternative routes of administration, including intratumoral brain infusion (ClinicalTrials.gov: NCT03911388 and NCT02457845).

The application of adaptive cell therapy using CAR T cells in brain tumors is also an area of rapid development. While CAR T cell therapy is primarily FDA approved for hematologic malignancies, the immunosuppressive tumor microenvironment in solid cancers, such as glioma, presents significant challenges. Current phase 1 and 2 clinical trials are investigating CAR T cells modified to recognize tumor-associated antigens, such as interleukin (IL)-13Rα2, HER2, and EGFRvIII, in glioma. These trials have demonstrated a favorable safety profile, with low toxicity and evidence of CAR T cell trafficking to the brain. One approach under investigation to enhance treatment response is the locoregional administration of CAR T cells directly into the tumor. Another approach involves combining CAR T cells with other treatment modalities, such as checkpoint inhibitors like anti-PD-1 (ClinicalTrials.gov: NCT03726515).

Currently, there are only a few preclinical or clinical trials investigating the combination of CAR T cells with oncolytic virotherapy, highlighting the novelty of the study by Tonne and colleagues in the field of brain tumor research. However, the use of an immunocompromised mouse model (NSG mice) in this study presents limitations for data analysis concerning tumor microenvironment remodeling and immune infiltration in glioma, which is known for its strong immunosuppressive characteristics. As the authors also noted, the use of oFV in glioma may not be the optimal combination due to the virus's slow replication rate and the rapid proliferation of the U251 glioma cell line both *in vitro* and *in vivo*. Nonetheless, the oFV virus serves as an excellent platform for generating chronic and long-lasting

infections, creating a balance between oncolysis and viral clearance.

In summary, while the combination of oFV with CAR T cell therapy presents certain challenges, the findings underscore the potential of oFV as an oncolytic platform. Further research is necessary to explore strategies that could enhance the persistence and efficacy of OVs in the tumor microenvironment, potentially through the integration of additional therapeutic approaches.

DECLARATION OF INTERESTS

The author declares no potential conflicts of interest.

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